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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/868,305	08/20/2001	Markus Albers	LEA33324	9002

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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 01/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/868,305	ALBERS ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-21 and 23* is/are pending in the application.

4a) Of the above claim(s) *5-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,12-21 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to an election of species filed on 11/19/02. There are twenty-two claims pending and sixteen under consideration. Claims 1-4 are compound claims. Claim 19 is a composition claim. Claims 20, 21, and 23 are use claims. Claims 12-18 are synthesis claims. This is the first action on the merits. The application concerns some biphenylene compounds, compositions, and uses thereof.

Election/Restrictions

2. Applicant's election of Group I in Paper No. 6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Applicants elected the species of example 18.1.3. This compound has R^2 = $NR^{2'}SO_2$. Claims 5-10, drawn to compounds with R^2 = hydrogen, alkyl, or phenyl are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 6.

4. Objection is made to claims 1, 2, 12-21 and 23 as containing non-elected subject matter. The claimed compounds, compositions, and methods that employ them present a variable core. Formula (1) contains compounds drawn to the non-

elected species to the extent that they read upon R^2 other than that of claim 3. The R^2 of claim 3 represents the limits of the present prior art search.

Claim Objections

5. Claim 4 is objected to because of the following informalities: in the third line of Applicants' recently submitted amendment the two words "fluoro residues" have been combined. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 12-21, and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1, 12, 21 contain the phrase "general formula (1)". This is indefinite because the word general implies more than one formula is being claimed. The Examiner suggests removing the word "general".

7. Claims 1, 12, 19, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Throughout these claims, Applicants list "substituted" alkyl, aryl, heterocyclic *etc* residues in their definitions of R^1-$R^{2'}$, R^3, and R^4. What substituents are intended? For

example, the specification in lines 15-26, page 46 describes the ester group (which is R^1). Nowhere are the possible substituents defined. The passage spanning line 19, page 48 to line 29, page 49 defines the substituent on the alkylene chain connected to ring A (which is R^2). The passage spanning line 9, page 65 to line 20, page 66 defines R^3 and R^4. In each instance, Applicants defines possible substituents using open terms. Lines 12-28, page 49, defining possible substituents on the claimed R^2 residues uses "such as", "optionally substituted amino", "a keto group", "an ester group, an amide group, a sulfoxide group, or a sulfone group". What substituents are being claimed?

8. Claims 1, 12, 19, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Throughout these claims, Applicants list "alkinyl residue". The phrase occurs in line 25, page 48 of the specification but is not further defined. Is the alkynyl radical, containing a carbon-to-carbon triple bond, intended?

9. Claims 1-4, 12-21, and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The definitions of R^3-R^6 indicate that two of these radicals may form a ring "which contain further

heteroatoms". What heteroatoms are permitted? Are they oxygen, nitrogen, and sulfur or is a metal or a halogen permitted? What is the size of this ring? Is there any limit? What other atoms are intended? How many additional non-carbon atoms may be present? For example in the passage spanning line 5, page 61 to line 2, page 62, Applicants describe the ring formed by R^3 and R^4. Applicants use open language "can be selected from the following nonexclusive list:". The following structures are five to seven-membered and contain a single nitrogen, sulfur, or oxygen atom. Is this all?

10. Claims 2-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Throughout these claims the three phrases "benzoyl or a substituted derivative thereof", "tolyl or a substituted derivative thereof, for example" and "tolyl or a substituted derivative thereof" occur. These are indefinite for four reasons. Firstly, "for example" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Secondly, it is unclear if the derivatives are of benzoyl and tolyl or the other recited radicals occurring earlier in the list. In lines 1 and 2, page 6 of Applicants recent amendments the punctuation would indicate that only benzoyl derivates are claimed. However,

lines 7-8, page 4 are ambiguous. Thirdly, the Examiner can find no list of derivates in the specification which made be made to a benzoyl or tolyl radical. Fourthly, some of listed examples could be considered tolyl derivatives, i.e. 2-methoxyphenyl and 4-trifluorophenyl but others could not, i.e. 2-chlorophenyl. This further clouds the issue of restricting the derivatives to tolyl. The Examiner suggests removing everything except benzoyl and tolyl as appropriate.

11. Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specification does not set forth any steps involved in determining how to identify "a integrin-mediated disease". It is unclear what diseases and treatments applicant is intending to encompass. Nowhere is the phrase defined. In the passage spanning line 23, page 1 to line 28, page 2 list some various diseases in connection with other $\alpha_v\beta_3$ antagonists. Lines 9-16, page 87 lists some various diseases that Applicants intend to treat. Are these all the "integrin-mediated disease[s]" or are there more? Identifying which diseases applicants intend this claim to cover will involve extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases applicants intend to treat, one skilled in the art cannot determine the metes and bounds of the claim. Hence, the claims are indefinite.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20, 21, and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating specific diseases, does not reasonably provide enablement for preventing any disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants are not enabled for preventing any of these diseases. The only established prophylactics are vaccines not the biphenylene carboxylic acid analogs such as present here. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of respiratory diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. In addition, it is presumed that "prevention" of the claimed diseases would require a method of identifying

those individuals who will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted. The Examiner suggests deletion of the word "preventing".

13. Claims 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating osteolytic diseases and restenosis, does not reasonably provide enablement for inhibiting angiogenesis generally, treating cancer generally or ophthalmic diseases generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. According to the On-line Medical Dictionary at http://cancerweb.ncl.ac.uk/omd/index.html, angiogenesis is "The process of vascularisation of a tissue involving the development of new capillary blood vessels." As such it is a normal process occurring in healthy tissue, particular during development. This claim would read on inhibiting angiogenesis in mammals with below normal angiogenesis activity, inhibiting angiogenesis in mammals with normal angiogenesis activity, or in asymptomatic mammals with up-regulated angiogenesis activity. The specification fails to teach any benefit to be gained from such actions. In fact, those actions would sound dangerous.

14. Evidence involving a single compound and two types of cancer was not found sufficient to establish the enablement of claims directed to a method of treating seven types of cancer with members of a class of several compounds *In re Buting* 163 USPQ 689.

To make clearer the lack of enablement for treatment of all cancer, extrinsic evidence is supplied by Draetta (Ann. Reports Med. Chem.), final sentence on page 246 "Although many still think about the need for a magic bullet as a cure for all cancers, our knowledge of the molecular mechanism underlying this disease make the prospect of developing such a universal cure very unlikely." Since no universal cure for cancer has been developed, it follows that there is no correlation between the assays relied upon by applicants and the ability to treat all cancers. Thus, those assays are not sufficient to enable such claims.

The remarkable advances in chemotherapy have seen the development of specific compounds to treat specific types of cancer. The great diversity of diseases falling within the "cancer" category means that it is contrary to medical understanding that any agent (let alone a genus of thousands of compounds) could be generally effective against such diseases. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task.

15. All the word "ophthalmic" indicates is that the disease process occurs in the eye. The class of diseases included under "ophthalmic disorders" would include cataracts, acute contagious conjunctivitis, myopia, tumors, diabetic retinopathy, and glaucoma. A diverse array of problems that arise from different sources. There is no such thing as being able to treat such widely diverse problems that arise from different sources.

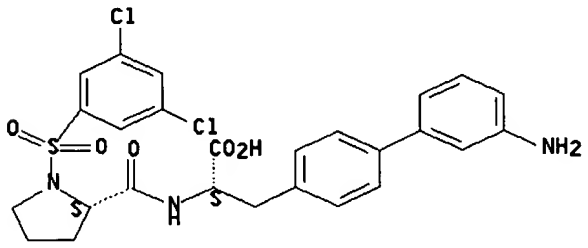
Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1, 12, 14, 19, 20, 21, and 23 are rejected under 35 U.S.C. 102(e) as being anticipated by Durette ('511). The compound shown below fits formula (1) with R^1 = H, $R^2 = NR^{2'}COR^{2'}$, $R^{2'}$ = hydrogen and the heterocycle pyrrolidine substituted by 3,5-dichlorophenyl)sulfonyl, U = W = a direct bond, V= the alkylene group CH_2, A = 1,4-phenylene, B = 1,3-phenylene, and $R^3 = R^4$ = hydrogen. It has

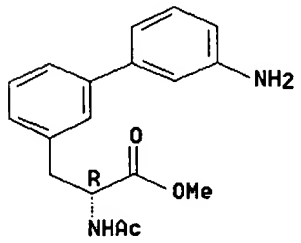
Registry Number 217325-22-9 and is found in claim 8, column 53, lines 59-60 of the reference. Claim 11 of the reference is drawn to compositions.



The synthesis of compound (16) is described in lines 32-36, column 26. The synthesis fits the limitations of Applicants formulas (2) and (3) with L = iodine and M = the organometallic residue boronic acid. The palladium compound used is described in line 57, column 24. The phosphane is triphenylphosphine. Thus, Applicants claims 12 and 14 are anticipated. Claim 9 of the reference teaches treatment of cell-adhesion mediated disorders. Line 9, column 4 of the reference suggests that "melanomas, carcinomas, and sarcomas" are included in the term. Thus, Applicants' claim for cancer treatment is anticipated. Claim 10 of the reference teaches treatment of arteriosclerosis and inflammation. Thus, anticipating Applicants' claim 23.

17. Claims 1-3, 12, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Burk (Journal of the American Chemical Society). The compound shown below fits formula (1) with $R^1 = CH_3$, $R^2 = NR^{2'}COR^{2'}$, $R^{2'}$ = hydrogen and

methyl, U = W = a direct bond, V= the alkylene group CH_2, A = B = 1,3-phenylene, and $R^3 = R^4$ = hydrogen. It has Registry Number 164460-72-4 and is found in Scheme 1, page 10847 of the reference. The first complete sentence in the paragraph below the figure states that the A = 1,4-phenylene isomer was also made. The synthesis of the compound is described in the second formula in Scheme 1. The synthesis fits the limitations of Applicants' formulas (2) and (3) with L = bromine and M = the organometallic residue boronic acid. The palladium compound used is palladium acetate. The phosphane is tri(ortho-tolyl)phosphine. Thus, Applicants' claims 12 and 14 are anticipated.



Double Patenting

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214

USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 19-21, and 23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,420,396 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compound of claim 1 of U.S. Patent No. 6,420,396 B1 is a species embraced by the generic formula of the present claim 1. According to the MPEP §806.04(i) "Generic Claims Presented for First Time After Issue of Species. The Office no longer follows the practice of prohibiting the allowance of generic claims that are presented for the first time after the issuance of a copending application claiming plural species. Instead, the Office may reject the generic claims on the grounds of obviousness-

type double patenting. Applicant may overcome such a rejection by filing a terminal disclaimer. See *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29."

19. Claims 1-4, 12-21, and 23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 12-18, 23, and 34-41 of copending Application No. 09/828,514. Although the conflicting claims are not identical, they are not patentably distinct from each other because except for the addition of $R^{2"}$ = hydrogen and the addition of a proviso to claim 1 of copending Application No. 09/828,514, the Examiner can see no difference between the two claims 1. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Allowable Subject Matter

20. The following is a statement of reasons for the indication of allowable subject matter: Applicants have defined restenosis in lines 24-25, page 1 as that occurring after angioplasty. Thus, no enablement rejection concerning the issue of restenosis will be made.

Conclusion

21. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for before final

amendments is (703) 872-9306. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

for **Mukund Shah**
Supervisory Patent Examiner
Art Unit 1624

TCMcK
January 7, 2003

JOHN M. FORD
PRIMARY EXAMINER
GROUP - ART UNIT 1624